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property data  
NEWS 16 MAR 01 INSPEC reloaded and enhanced  
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reserved on STN DUPLICATE 1  
AN 2006139070 EMBASE  
TI Modelling and imaging cardiac repolarization abnormalities.  
AU Rudy Y.  
CS Dr. Y. Rudy, Washington University in St. Louis, Cardiac Bioelectricity  
Center, 290 Whitaker Hall, St Louis, MO 63130-4899, United States.  
rudy@wustl.edu  
SO Journal of Internal Medicine, (2006) Vol. 259, No. 1, pp. 91-106. .  
Refs: 47  
ISSN: 0954-6820 E-ISSN: 1365-2796 CODEN: JINMEO  
CY United Kingdom  
DT Journal; Conference Article  
FS 006 Internal Medicine  
014 Radiology  
018 Cardiovascular Diseases and Cardiovascular Surgery  
027 Biophysics, Bioengineering and Medical Instrumentation  
LA English  
SL English  
ED Entered STN: 11 Apr 2006  
Last Updated on STN: 11 Apr 2006  
AB Repolarization abnormalities, including those induced by the congenital or  
acquired long QT ( \*\*\*LQT\*\*\* ) syndrome, provide a substrate for  
life-threatening cardiac arrhythmias. In this article, we use  
computational biology to link \*\*\*HERG\*\*\* \*\*\*mutations\*\*\*  
mechanistically to the resulting abnormalities of the whole-cell action  
potential. We study how the kinetic properties of I(Ks) (the slow delayed  
rectifier) that are conferred by molecular subunit interactions,  
facilitate its role in repolarization and 'repolarization reserve'. A new  
noninvasive imaging modality (electrocardiographic imaging) is shown to  
image cardiac repolarization on the epicardial surface, suggesting its  
possible role in risk stratification, diagnosis and treatment of  
\*\*\*LQT\*\*\* syndrome. .COPYRGT. 2005 Blackwell Publishing Ltd.

L4 ANSWER 2 OF 36 CAPLUS COPYRIGHT 2006 ACS ON STN  
AN 2005:1019605 CAPLUS  
DN 144:105520  
TI A novel splice \*\*\*mutation\*\*\* of \*\*\*HERG\*\*\* in a Chinese family  
with long QT syndrome  
AU Shang, Yun-peng; Xie, Xu-dong; Wang, Xing-xiang; Chen, Jun-zhu; Zhu,  
Jian-hua; Tao, Qian-min; Zheng, Liang-rong  
CS Department of Cardiovascular Diseases, First Affiliated Hospital, School  
of Medicine, Zhejiang University, Hangzhou, 310003, Peop. Rep. China  
SO Journal of Zhejiang University, Science, B (2005), 6B(7), 626-630  
CODEN: JZUSAM  
PB Zhejiang University Press  
DT Journal  
LA English  
AB Congenital long QT syndrome (LQTS) is a genetically heterogeneous disease  
in which six ion-channel genes have been identified. The  
phenotype-genotype relationships of the HERG (human ether-a-go-go-related  
gene) mutations are not fully understood. The objective of this study is  
to identify the underlying genetic basis of a Chinese family with LQTS and  
to characterize the clin. manifestations properties of the mutation.  
Single strand conformation polymorphism (SSCP) analyses were conducted on  
DNA fragments amplified by polymerase chain reaction from five \*\*\*LQT\*\*\*  
-related genes. Aberrant conformers were analyzed by DNA sequencing. A  
novel splice mutation in C-terminus of HERG was identified in this Chinese  
LQTS family, leading to the deletion of 11-bp at the acceptor splice site  
of Exon9 (Exon9 IVS del (-12.fwdarw.-2)). The mutation might affect,  
through deficient splicing, the putative cyclic nucleotide binding domain  
(CNBD) of the HERG K+ channel. This mutation resulted in a mildly  
affected phenotype. Only the proband had a history of syncope, while the  
other three individuals with long QT interval had no symptoms. Two other  
mutation carriers displayed normal phenotype. No sudden death occurred in  
the family. The 4 affected individuals and the two silent mutation  
carriers were all heterozygous for the mutation. It is the first splice  
\*\*\*mutation\*\*\* of \*\*\*HERG\*\*\* reported in Chinese LQTS families.  
Clin. data suggest that the CNBD mutation may be less malignant than  
mutations occurring in the pore region and be partially dominant over  
wild-type function.

RE.CNT 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD  
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- L4 ANSWER 3 OF 36 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN  
AN 2004:172928 BIOSIS  
DN PREV200400174045  
TI Gating and drug binding properties of A653-HERG, a highly conserved residue in K<sup>+</sup> channels.  
AU Stepanovic, Svetlana Z. [Reprint Author]; Petersen, Christina I. [Reprint Author]; Balser, Jeffrey R. [Reprint Author]  
CS Anesthesiology, Vanderbilt University, Nashville, TN, USA  
SO Biophysical Journal, (January 2004) Vol. 86, No. 1, pp. 522a. print.  
Meeting Info.: 48th Annual Meeting of the Biophysical Society, Baltimore, MD, USA, February 14-18, 2004. Biophysical Society.  
ISSN: 0006-3495 (ISSN print).  
DT Conference; (Meeting)  
Conference: Abstract; (Meeting Abstract)  
LA English  
ED Entered STN: 31 Mar 2004  
Last Updated on STN: 31 Mar 2004  
AB HERG encodes a K<sup>+</sup> channel involved in repolarization of the cardiac action potential. Congenital \*\*\*mutations\*\*\* in \*\*\*HERG\*\*\* that reduce delayed rectifier (IKr) current, and direct block of IKr by various pharmacological agents, evoke the long QT (\*\*\*LQT\*\*\*) syndrome, a condition that can lead to life-threatening arrhythmias. We studied mutations of an alanine residue, HERG-653A, conserved in all K<sup>+</sup> channels. This alanine is located 5 residues downstream of the 'glycine hinge' implicated in K<sup>+</sup> channel opening, and is near the 652Y and 656F residues implicated in drug binding to HERG. Mutant channels were expressed in *Xenopus* oocytes for analyzing gating and drug binding properties. Threonine(T), valine(V) and tyrosine(Y) substitutions evoked marked (gtoreq-50mV) hyperpolarization shifts in the voltage-dependence of activation (V1/2). For WT-HERG V1/2 was -26+-1.4 mV versus -83+-1.3, -76+-1.2, -85+-1.4 for T, V, Y, respectively (p<0.001). Cysteine(C), isoleucine(I), glycine(G) and serine(S) exhibited WT-like gating, with modest (<-25mV) shifts in V1/2 compared to WT-HERG. All mutants further hyperpolarized oocyte resting potential compared to WT-HERG. Inactivation gating and reversal potentials were not significantly altered in any of the 7 mutants. Mutants with large negative shift in V1/2 were constitutively open at all potentials, except for the inactivation gating, and did not display typical deactivation 'tail' currents. These mutants exhibit large inward current at membrane potentials below Erev (-82 mV). While alanine substitution disrupted dofenitide binding, as expected for an S6 mutation, these effects were greatest in T, Y, G (5-20% block versus 75% block for WT-HERG in 1 muM dofenitide) suggesting that the gating effects of A653 are not closely linked to the drug receptor properties. Our study reveals the importance of a conserved residue in K<sup>+</sup> channels, which destabilizes the closed state, as reported in CNG1 channel.
- L4 ANSWER 4 OF 36 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN  
AN 2004:124224 BIOSIS  
DN PREV200400127158  
TI Truncation mutation P872fs877 in the C-terminus of the hERG potassium channel causes \*\*\*LQT\*\*\* by trafficking problems of heterotetrameric channels.  
AU Raes, Adam L. [Reprint Author]; Paulussen, Aimee D. C.; Aerssens, Jeroen; Snyders, Dirk J. [Reprint Author]  
CS Biomedical Sciences, University of Antwerp, Antwerp, Belgium  
SO Biophysical Journal, (January 2004) Vol. 86, No. 1, pp. 279a. print.  
Meeting Info.: 48th Annual Meeting of the Biophysical Society, Baltimore, MD, USA, February 14-18, 2004. Biophysical Society.  
ISSN: 0006-3495 (ISSN print).  
DT Conference; (Meeting)  
Conference: Abstract; (Meeting Abstract)  
LA English  
ED Entered STN: 3 Mar 2004  
Last Updated on STN: 3 Mar 2004  
AB \*\*\*Mutations\*\*\* in the KCNH2 (\*\*\*HERG\*\*\*) gene are responsible for the long QT syndrome (LQTS) by alterations of the delayed rectifier current IKr, thus delaying cardiac repolarization and rendering patients vulnerable to ventricular arrhythmias and sudden death. We identified and characterized a mutation (P872fs877) in the C-terminus of the KCNH2 gene in a large Dutch LQTS family. The mutation leads to a premature stop codon causing a C-terminal truncation of the protein. Biochemical and confocal microscopy techniques were used to investigate protein expression and trafficking. The biophysical properties of hERG channels were assayed by electrophysiological methods. The P872fs877 protein was clearly present in the membrane as determined by confocal microscopy. Homotetrameric expression of P872fs877 channels produced currents with minor changes in the biophysical properties and with only a small reduction in amplitude compared to WT. During voltage clamp experiments with action potential waveforms no significant differences were observed between WT and P872fs877. However, upon co-expression of WT and P872fs877 subunits, the fraction of hERG channels generating the current during action potential clamp experiments increased from approx 30% for WT and mutant to 70% for the heterotetramers. As a consequence, this increased repolarizing power during the action potential, only observed with heterotetramers of this C-terminal \*\*\*HERG\*\*\* \*\*\*mutation\*\*\* and WT subunits, should shorten the QT intervals. However, confocal

microscopy revealed that the heterotetramers were largely retained in the ER. This dominant negative effect appears to predominate over the apparent increase in repolarizing power, thus explaining the LQTS phenotype.

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AN 2004140112 EMBASE  
TI Clinical and electrophysiological characterization of a novel \*\*\*mutation\*\*\* R863X in \*\*\*HERG\*\*\* C-terminus associated with long QT syndrome.  
AU Teng S.; Ma L.; Dong Y.; Lin C.; Ye J.; Bahringer R.; Vardanyan V.; Yang Y.; Lin Z.; Pongs O.; Hui R.  
CS R. Hui, Sino-Ger. Lab. for Molec. Medicine, Fuwai Hospital, Peking Union Medical College, 167 Beilishilu, 100037 Beijing, China. huirutai@sglab.org  
SO Journal of Molecular Medicine, (2004) Vol. 82, No. 3, pp. 189-196. .  
Refs: 29  
ISSN: 0946-2716 CODEN: JMLME8  
CY Germany  
DT Journal; Article  
FS 018 Cardiovascular Diseases and Cardiovascular Surgery  
022 Human Genetics  
LA English  
SL English  
ED Entered STN: 12 Apr 2004  
Last Updated on STN: 12 Apr 2004  
AB We have found a novel nonsense mutation in the C-terminus of HERG in a four-generation Chinese family with long QT syndrome and investigated the molecular mechanism of this mutation in vitro. Six family members, including the proband, were clinically affected. Syncope and ventricular tachycardia of torsades de pointes were triggered by startling or emotional stress, and beta-adrenergic blockade treatment was ineffective. Haplotype analysis showed that only \*\*\*LQT\*\*\* (2) markers cosegregated with the disease, and sequence analysis revealed a substitution of T with C at nucleotide position 2770 of the HERG gene (U04270), which creates a stop codon at amino acid position 863 (R863X) of the HERG protein, leading to a deletion of 296 amino acids. Whole cell patch clamp studies showed that the R863X HERG could not induce time-dependent current. Coexpression of R863X with wild-type HERG showed reduced current densities and accelerated voltage-dependent inactivation of HERG channels. Subcellular localization of R863X-EGFP revealed that the mutant did not traffic to the cell surface. These data suggest that R863X failed to form functional HERG channels, contributing to a prolongation of the QT interval and long QT syndrome with a dominant phenotype. These findings provide new insights into the structure-function relationships of the HERG C-terminus.
- L4 ANSWER 6 OF 36 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN  
AN 2005:523695 BIOSIS  
DN PREV200510313658  
TI A common antitussive drug, dobutinol, precipitates the long-QT2 syndrome.  
AU Bellocq, Chloe [Reprint Author]; Wilders, Ronald; Scholt, Jean-Jacques; Louerat-Onou, Benedicte; Boisseau, Pierre; Le Marec, Herve; Escande, Denis; Baro, Isabelle  
CS INSERM, U533, Inst Thorax, Nantes, France  
SO Circulation, (OCT 26 2004) Vol. 110, No. 17, Suppl. S, pp. 17.  
Meeting Info.: 77th Scientific Meeting of the American-Heart-Association, New Orleans, LA, USA, November 07 -10, 2004. Amer Heart Assoc.  
CODEN: CIRCAZ. ISSN: 0009-7322.  
DT Conference; (Meeting)  
Conference: Abstract; (Meeting Abstract)  
LA English  
ED Entered STN: 1 Dec 2005  
Last Updated on STN: 1 Dec 2005  
AB QT prolongation, a classical risk factor for arrhythmias can result from a mutation in one of the genes governing cardiac repolarization and also can result from the intake of a medication acting as blocker of the cardiac K<sup>+</sup> channel HERG. A 9-year boy diagnosed with congenital long QT2 syndrome (QTc = 597 ms), experienced for the first time torsade-de-pointe arrhythmias while being treated with dobutinol, a commonly used non-opioid antitussive drug. The arrhythmia ceased after the drug was discontinued. In the proband, we identified a novel A561P \*\*\*HERG\*\*\* \*\*\*mutation\*\*\*. Both his father and brother are also mutation carrier with a long QT but never experienced syncope or arrhythmia. Two others \*\*\*LQT\*\*\* mutations (A561V and A561T) had previously been reported at the same position. Neither of the three HERG mutants led to sizeable current in heterologous expression system. When co-expressed with wild-type (WT) HERG channels, the three A561 mutants reduced the trafficking of WT and mutant heteromeric channels resulting in decreased K<sup>+</sup> current amplitude (dominant-negative effects). In addition, A561P but not A561V and A561T mutants induced a -11-mV shift in the HERG current activation curve and accelerated deactivation, thereby partially counteracting the dominant-negative effects. Using the patch-clamp technique, we showed that dobutinol dose-dependently inhibited the HERG K<sup>+</sup> current with a half-maximum block concentration of 2.9 10(-6) M and a Hill coefficient of 0.9. The effects of the A561P mutation and dobutinol on the human ventricular action potential characteristics were simulated using the Priebe-Beuckelmann computer model. A prolongation of the action potential duration (APD(90)) from 357 to 463 ms (cycle length: 1000 ms) resulted from the A561P \*\*\*HERG\*\*\* \*\*\*mutation\*\*\*. Dobutinol, at circulating therapeutic drug concentrations, induced a further APD(90) prolongation from 463 to 503 ms. At the same concentration, dobutinol

prolonged the WT-HERG APD(90) from 357 to 393 ms. Our work shows that a common drug not previously identified as a QT prolonging drug can precipitate the LQT2 syndrome. The drug is not expected to produce clinically relevant effects in individuals with normal cardiac repolarization reserve.

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AN 2003431989 EMBASE

TI [Comparison of Different Formulas of QT Interval Correction in \*\*\*LQT\*\*\* Families During Exercise].

SROVNANI RUZNYCH METOD KOREKCE QT INTERVALU PRI ZATEZI V RODINACH SE

SYNDROMEM DLOUHEHO QT INTERVALU.

AU Sisakova M.; Vlasinova J.; Semrad B.; Chroust K.; Ravcukova B.

CS Dr. M. Sisakova, Interní Kardiologická Klinika, FN Brno, Jihlavská 20, 639 00 Brno, Czech Republic

SO Vnitřní Lekarství, (2003) Vol. 49, No. 10, pp. 799-801. .

Refs: 13

ISSN: 0042-773X CODEN: VNLEAH

CY Czech Republic

DT Journal; Article

FS 006 Internal Medicine

018 Cardiovascular Diseases and Cardiovascular Surgery

LA Czech

SL English; Czech

ED Entered STN: 13 Nov 2003

Last Updated on STN: 13 Nov 2003

AB Background: Pathologic prolongation of QT interval is related to increased risk of arrhythmias. Changes of this parameter are influenced by many conditions, the most important is heart rate. Several formulas have been proposed for mathematical description of QT interval/heart rate relationship. The aim of this study was comparison of different QT interval correction formulas in families with congenital long QT syndrome (LQTS). Methods: In 28 members of 6 families with LQTS occurrence bicycle ergometry testings were performed. QT and RR intervals were measured before exercise, at peak exercise and in the 1st and the 6th minute of restitution. For QT interval correction single-parameter formulas by Bazett, Fridericia, Malik and Framingham study were used. In 3 families the results could be correlated with genetically proved diagnosis (KCNQ1 gene \*\*\*mutations\*\*\* in 2 families, \*\*\*HERG\*\*\* -KCNH2 gene \*\*\*mutation\*\*\* in the other). Results: In the described group the genetically established diagnosis of LQTS correlated at best with values obtained with correction by Bazett. All the mutation carriers were correctly identified only by this method. The Fridericia, Malik and Framingham formulas failed to identify 2 patients - mutation carriers (both KCNQ1 and \*\*\*HERG\*\*\* -KCNH2 \*\*\*mutations\*\*\* ). Discussion: Because of simplicity the Bazett formula remains the most common method of QT interval correction. Moreover, in our study this formula appeared to be the most sensitive for clinical diagnosis of LQTS.

L4 ANSWER 8 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN

AN 2002:562791 CAPLUS

DN 138:100652

TI Pharmacological rescue of human K+ channel long-QT2 mutations: human ether-a-go-go-related gene rescue without block

AU Rajamani, Sridharan; Anderson, Corey L.; Anson, Blake D.; January, Craig T.

CS Department of Medicine (Cardiology), University of Wisconsin, Madison, WI, USA

SO Circulation (2002), 105(24), 2830-2835

CODEN: CIRCAZ; ISSN: 0009-7322

PB Lippincott Williams & Wilkins

DT Journal

LA English

AB Background-Defective protein trafficking is a consequence of gene mutations. Human long-QT ( \*\*\*LQT\*\*\* ) syndrome results from mutations in several genes, including the human ether-a-go-go-related gene (HERG), which encodes a delayed rectifier K+ current. Trafficking-defective mutant HERG protein is a mechanism for reduced delayed rectifier K+ current in LQT2, and high-affinity HERG channel-blocking drugs can result in pharmacol. rescue. Methods and Results-We postulated that drug mols. modified to remove high-affinity HERG block may still stabilize mutant proteins in a conformation required for rescue. The authors tested terfenadine carboxylate (fexofenadine) and terfenadine, structurally similar drugs with markedly different affinities for HERG block, for rescue of trafficking-defective LQT2 mutations. Terfenadine rescued the N470D mutation but blocked the channels. In contrast, fexofenadine rescued N470D with a half-maximal rescue concn. of 177 nmol/L, which is approx. 350-fold lower than the half-maximal channel block concn. The G601S mutation was also rescued without channel block. Conclusions-Pharmacol. rescue can occur without channel block. This could represent a new antiarrhythmic paradigm in the treatment of some trafficking-defective LQT2 mutations.

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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN

AN 2001:803588 CAPLUS

DN 137:4167

TI Mutation detection in long QT syndrome: A comprehensive set of primers and PCR conditions

AU Syrris, P.; Murray, A.; Carter, N. D.; McKenna, W. M.; Jeffery, S.

CS Medical Genetics Unit, St George's Hospital Medical School, London, SW17 0RE, UK

SO Journal of Medical Genetics (2001), 38(10), 705-710

CODEN: JMDGAE; ISSN: 0022-2593

PB BMJ Publishing Group

DT Journal

LA English

AB A robust and reproducible set of primers was produced for polymerase chain reaction (PCR)/single-strand conformation polymorphism (SSCP) anal. of all five genes involved in the long QT ( \*\*\*LQT\*\*\* ) syndrome. The ext. PCR conditions were defined for a successful amplification of every PCR fragment, which allowed effective mutational anal. of the five known \*\*\*LQT\*\*\* genes. All KCNQ1 exons were amplified without using formamide, instead, using PCR methods, \*\*\*mutation\*\*\* screening of \*\*\*HERG\*\*\* was obtained by amplifying only 19 fragments compared to 20 and 24 by recombining existing primers in a more effective way and then optimizing PCR conditions for each fragment. Four known polymorphisms and two novel changes on KCNQ1 and KCNE1 were obsd. in the evaluation using DNA samples from sudden death cases and controls. In the first gene, two single nucleotide polymorphisms (SNPs) at amino acid positions 546 and 642 and a novel one at position 308 were detected, while a novel SNP and a two known polymorphisms at positions 38 and 85 were detected in KCNE1.

RE.CNT 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN

AN 2000:98826 CAPLUS

DN 132:162048

TI Mutations in and genomic structure of HERG - a long QT syndrome gene, and \*\*\*LQT\*\*\* diagnosis

IN Keating, Mark T.; Splawski, Igor

PA University of Utah Research Foundation, USA

SO PCT Int. Appl., 164 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI WO 2000006772	A1	20000210	WO 1999-US16337	19990720
W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW			
RW:	GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			

US 6207383	B1	20010327	US 1999-226012	19990106
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CA 2336236	AA	20000210	CA 1999-2336236	19990720
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AU 9951133	A1	20000221	AU 1999-51133	19990720
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AU 774194	B2	20040617		
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EP 1102863	A1	20010530	EP 1999-935710	19990720
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JP 2002521065	T2	20020716	JP 2000-562554	19990720
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AU 2004202006	A1	20040610	AU 2004-202006	20040511
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PRAI US 1998-122847 A 19980727

US 1999-226012 A 19990106

WO 1999-US16337 W 19990720

AB The invention relates to the detn. of the genomic structure of HERG, a gene assocd. with long QT syndrome, construction of primers for \*\*\*mutational\*\*\* anal. of \*\*\*HERG\*\*\*, and newly identified \*\*\*mutations\*\*\* in \*\*\*HERG\*\*\*. Methods of diagnosis of mutations causing long QT syndrome using nucleic acid probe hybridization, single stranded conformation polymorphism technique, gene sequencing and amplification, RNase assay are also described. Also disclosed are methods of diagnosis of long QT syndrome via immunocytochem. technique and immunoblotting with antibodies raised against a mutant HERG polypeptide, and a method of amplifying an exon of HERG using oligonucleotide primers. A method of screening for drugs useful in treating a person with \*\*\*mutation\*\*\* in \*\*\*HERG\*\*\* via measurement of a first induced K+ current in cells transformed with HERG and a transgenic animal are also provided. The sequences of the 15 intron/exon junctions has been detd. and this information is useful in devising primers for amplifying and sequencing across all of the exons of the gene. This is useful for detg. the presence or absence of mutations which are known to cause long QT syndrome. Also disclosed are many new \*\*\*mutations\*\*\* in \*\*\*HERG\*\*\* which have been found to be assocd. with long QT syndrome. Linkage anal. and phys. and genetic mapping was used to localize HERG to human chromosome 7q35-36 region. Northern blot anal. revealed that HERG is expressed mainly in heart. Combined with sequence homol. data and assocn. of mutation and \*\*\*LQT\*\*\*, it was suggested that HERG encodes alpha-subunit of potassium channel.

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

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AN 2000390094 EMBASE

DUPLICATE 2

TI A structural basis for drug-induced long QT syndrome.  
 AU Mitcheson J.S.; Chen J.; Lin M.; Culbertson C.; Sanguinetti M.C.  
 CS M.C. Sanguinetti, Eccles Institute of Human Genetics, University of Utah,  
 Salt Lake City, UT 84112, United States. mike.sanguinetti@hdc.utah.edu  
 SO Proceedings of the National Academy of Sciences of the United States of  
 America, (24 Oct 2000) Vol. 97, No. 22, pp. 12329-12333. .  
 Refs: 33  
 ISSN: 0027-8424 CODEN: PNASA6  
 CY United States  
 DT Journal; Article  
 FS 018 Cardiovascular Diseases and Cardiovascular Surgery  
 029 Clinical Biochemistry  
 037 Drug Literature Index  
 LA English  
 SL English  
 ED Entered STN: 13 Dec 2000  
 Last Updated on STN: 13 Dec 2000  
 AB \*\*\*Mutations\*\*\* in the \*\*\*HERG\*\*\* K+ channel gene cause inherited  
 long QT syndrome ( \*\*\*LQT\*\*\* ), a disorder of cardiac repolarization  
 that predisposes affected individuals to lethal arrhythmias [Curran, M.  
 E., Splawski, I., Timothy, K. W., Vincent, G. M., Green, E. D. and  
 Keating, M. T. (1995) Cell 80, 795-804]. Acquired \*\*\*LQT\*\*\* is far  
 more common and is most often caused by block of cardiac HERG K+ channels  
 by commonly used medications [Roden, D. M., Lazzara, R., Rosen, M.,  
 Schwartz, P. J., Towbin, J. and Vincent, G. M. (1996) Circulation 94,  
 1996-2012]. It is unclear why so many structurally diverse compounds  
 block HERG channels, but this undesirable side effect now is recognized as  
 a major hurdle in the development of new and safe drugs. Here we use  
 alanine-scanning mutagenesis to determine the structural basis for  
 high-affinity drug block of HERG channels by MK-499, a  
 methanesulfonamide antiarrhythmic drug. The binding site, corroborated  
 with homology modeling, is comprised of amino acids located on the S6  
 transmembrane domain (G648, Y652, and F656) and pore helix (T623 and  
 V625)  
 of the HERG channel subunit that face the cavity of the channel. Other  
 compounds that are structurally unrelated to MK-499, but cause \*\*\*LQT\*\*\*  
 , also were studied. The antihistamine terfenadine and a gastrointestinal  
 prokinetic drug, cisapride, interact with Y652 and F656, but not with  
 V625. The aromatic residues of the S6 domain that interact with these  
 drugs (Y652 and F656) are unique to eag/erg K+ channels. Other  
 voltage-gated K+ (Kv) channels have Ile and Val (Ile) in the equivalent  
 positions. These findings suggest a possible structural explanation for  
 how so many commonly used medications block HERG but not other Kv  
 channels  
 and should facilitate the rational design of drugs devoid of HERG channel  
 binding activity.  
 L4 ANSWER 12 OF 36 BIOSIS COPYRIGHT (c) 2006 The Thomson  
 Corporation on  
 STN DUPLICATE 3  
 AN 2000:452423 BIOSIS  
 DN PREV200000452423  
 TI The dominant negative LQT2 mutation A561V reduces wild-type HERG  
 expression.  
 AU Kagan, Anna; Yu, Zhihui; Fishman, Glenn I.; McDonald, Thomas V. [Reprint  
 author]  
 CS Section of Molecular Cardiology, Departments of Medicine and Molecular  
 Pharmacology, Albert Einstein College of Medicine, Bronx, NY, 10461, USA  
 SO Journal of Biological Chemistry, (April 14, 2000) Vol. 275, No. 15, pp.  
 11241-11248. print.  
 CODEN: JBCHA3. ISSN: 0021-9258.  
 DT Article  
 LA English  
 ED Entered STN: 25 Oct 2000  
 Last Updated on STN: 10 Jan 2002  
 AB HERG1 K+ channel mutations are responsible for one form of dominantly  
 inherited long QT syndrome ( \*\*\*LQT\*\*\* ). Some \*\*\*LQT\*\*\* mutations  
 exert a dominant negative effect on wild-type current expression. To  
 investigate mechanisms of dominant-negative behavior, we co-expressed  
 wild-type HERG with the A561V mutant in mammalian cells. Transfection  
 with various cDNA ratios produced HERG K+ current densities that  
 approached a predicted binomial distribution where mutant and wild-type  
 subunits co-assemble in a tetramer with nearly complete dominance. Using  
 C terminus myc-tagged wild-type HERG we specifically followed the mutant's  
 effect on full-length wild-type HERG protein expression. Co-expression  
 with A561V reduced the abundance of full-length wild-type HERG protein  
 comparable to the current reduction. Reduction of wild-type protein was  
 due to decreased synthesis and increased turnover. Conditions  
 facilitating protein folding (growth at 30 degreeC, or in 10% glycerol)  
 resulted in partial rescue from the dominant effect, as did the 26 S  
 proteasome inhibitor ALLN. Thus, for A561V, dominant negative effects  
 result from assembly of wild-type subunits with mutant very early in  
 production leading to rapid recognition of mutant channels and targeting  
 for proteolysis. These results establish protein misfolding, cellular  
 proofreading, and bystander involvement as contributing mechanisms for  
 dominant effects in LQT2.  
 L4 ANSWER 13 OF 36 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights  
 reserved on STN DUPLICATE 4  
 AN 2000289846 EMBASE  
 TI Identical twins with long QT syndrome associated with a missense mutation  
 in the S4 region of the HERG.  
 AU Hayashi K.; Shimizu M.; Ino H.; Okeie K.; Yamaguchi M.; Yasuda T.; Fujino  
 N.; Fujii H.; Fujita S.; Mabuchi H.  
 CS Dr. K. Hayashi, Second Department Internal Medicine, School of Medicine,  
 Kanazawa University, Takara-machi 13-1, Kanazawa 920-8640, Japan  
 SO Japanese Heart Journal, (2000) Vol. 41, No. 3, pp. 399-404. .  
 Refs: 20  
 ISSN: 0021-4868 CODEN: JHEJAR  
 CY Japan  
 DT Journal; Article  
 FS 006 Internal Medicine  
 018 Cardiovascular Diseases and Cardiovascular Surgery  
 022 Human Genetics  
 LA English  
 SL English  
 ED Entered STN: 7 Sep 2000  
 Last Updated on STN: 7 Sep 2000  
 AB Familial long QT syndrome (LQTS) is caused by mutations in genes encoding  
 ion channels important in determining ventricular repolarization.  
 Mutations in at least five genes have been associated with the LQTS. Five  
 genes, KCNQ1, HERG, SCN5A, KCNE1, and KCNE2, have been identified.  
 We  
 have identified a missense \*\*\*mutation\*\*\* in the \*\*\*HERG\*\*\* gene  
 in identical twins in a Japanese family with LQTS. The identical twins in  
 our study had QT prolongation and the same missense mutation. However  
 only the proband had a history of syncope. Although many mutations in  
 \*\*\*LQT\*\*\* genes have been reported, there are few reports of twins with  
 LQTS. This is the first report, to our knowledge, of identical twins with  
 a \*\*\*HERG\*\*\* gene \*\*\*mutation\*\*\* .  
 L4 ANSWER 14 OF 36 BIOSIS COPYRIGHT (c) 2006 The Thomson  
 Corporation on  
 STN  
 AN 2000:530282 BIOSIS  
 DN PREV200000530282  
 TI Notched T-waves on Holter recordings in long-QT syndrome: A phenotypic  
 marker of \*\*\*HERG\*\*\* missense \*\*\*mutation\*\*\* carriers.  
 AU Lupoglazoff, J. M. [Reprint author]; Denjoy, I.; Berthet, M.; Hainque, B.;  
 Villain, E.; Vaksman, G.; Klug, D.; Lucet, V.; Coumel, P.; Guicheney, P.  
 CS Pediatric Cardiology Dept., Robert Debre Hospital, Paris, France  
 SO European Heart Journal, (August-September, 2000) Vol. 21, No. Abstract  
 Supplement, pp. 353. print.  
 Meeting Info.: XXII Congress of the European Society of Cardiology.  
 Amsterdam, Netherlands. August 26-30, 2000. European Society of  
 Cardiology.  
 CODEN: EHJODF. ISSN: 0195-668X.  
 DT Conference; (Meeting)  
 Conference; Abstract; (Meeting Abstract)  
 LA English  
 ED Entered STN: 6 Dec 2000  
 Last Updated on STN: 11 Jan 2002  
 L4 ANSWER 15 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN  
 AN 1999:286083 CAPLUS  
 DN 130:307553  
 TI Cloning and expression of human Herg-2 and Herg-3 genes  
 IN Ganetzky, Barry S.; Titus, Steven A.  
 PA Wisconsin Alumni Research Foundation, USA  
 SO PCT Int. Appl., 46 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 FAN.CNT 1  

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9920760	A2	19990429	WO 1998-US22286	19981021
WO 9920760	A3	19990708		
W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,			
	DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG,			
	KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX,			
	NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT,			
	UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES,			
	FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI,			
	CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
US 5986081	A	19991116	US 1997-956242	19971022
AU 9911108	A1	19990510	AU 1999-11108	19981021
US 6087488	A	20000711	US 1999-351215	19990712
PRAI US 1997-956242	A	19971022		
WO 1998-US22286	W	19981021		
AB	This invention provides protein and cDNA sequences for newly identified Herg-2 and Herg-3 genes, which encode polypeptides believed to be of the human ERG ion-channel family. The proteins of the invention have approx. 85% homol. to the known human ERG potassium channel. Said cDNAs and proteins are of interest because ***mutations*** to the ***Herg*** gene can cause long-QT ( ***LQT*** ) syndrome, a relatively rare disorder that causes syncope and sudden death due to ventricular arrhythmia.			

 L4 ANSWER 16 OF 36 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights  
 reserved on STN DUPLICATE 5  
 AN 1999377572 EMBASE  
 TI Correction of defective protein trafficking of a mutant HERG potassium  
 channel in human long QT syndrome. Pharmacological and temperature  
 effects.

- AU Zhou Z.; Gong Q.; January C.T.  
 CS Z. Zhou, Section of Cardiology, Univ. of Wisconsin Hospitals/Clinics, 600 Highland Ave., Madison, WI 53792, United States. zhz@medicine.wisc.edu  
 SO Journal of Biological Chemistry, (29 Oct 1999) Vol. 274, No. 44, pp. 31123-31126.  
 Refs: 29  
 ISSN: 0021-9258 CODEN: JBCHA3  
 CY United States  
 DT Journal; Article  
 FS 018 Cardiovascular Diseases and Cardiovascular Surgery  
 029 Clinical Biochemistry  
 030 Pharmacology  
 037 Drug Literature Index  
 LA English  
 SL English  
 ED Entered STN: 18 Nov 1999  
 Last Updated on STN: 18 Nov 1999  
 AB The chromosome 7-linked form of congenital long QT syndrome (LQT2) is caused by mutations in the human ether-a-go-go-related gene (HERG) that encodes the rapidly activating delayed rectifier potassium channel. One mechanism for the loss of normal channel function in LQT2 is defective protein trafficking, which results in the failure of the channel protein to reach the plasma membrane. Here we show that the N470D LQT2 mutant protein is trafficking-deficient when expressed at 37 .degree.C in HEK293 cells, whereas at 27 .degree.C its trafficking to the plasma membrane and channel function are markedly improved. We further show that the antiarrhythmic drug E-4031, which selectively blocks HERG channels, also corrects defective protein trafficking of the N470D mutant and can restore the generation of HERG current. Similar findings were obtained with the drugs astemizole and disopride, as well as with high concentrations of glycerol. The effect of E-4031 on HERG protein trafficking was concentration-dependent and required low drug concentrations (saturation present at 5 .mu.M), developed rapidly with drug exposure, and occurred post-translationally. These findings suggest that protein misfolding leading to defective trafficking of some \*\*\*HERG\*\*\* \*\*\*LQT\*\*\* \*\*\*mutations\*\*\* may be corrected by specific pharmacological strategies.
- L4 ANSWER 17 OF 36 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 6  
 AN 1999108177 EMBASE  
 TI C-terminal \*\*\*HERG\*\*\* \*\*\*mutations\*\*\* : The role of hypokalemia and a KCNQ1-associated mutation in cardiac event occurrence.  
 AU Berthel M.; Denjoy I.; Donger C.; Demay L.; Hammoude H.; Klug D.; Schutze-Bahr E.; Richard P.; Funke H.; Schwartz K.; Coumel P.; Hainque B.; Guicheney P.  
 CS Dr. P. Guicheney, INSERM U153, Groupe Hospitalier Pitie-Salpetriere, 47 boulevard de l'Hopital, 75651 Paris Cedex 13, France. pguichen@myologie.infobiogen.fr  
 SO Circulation, (23 Mar 1999) Vol. 99, No. 11, pp. 1464-1470.  
 Refs: 31  
 ISSN: 0009-7322 CODEN: CIRCZ  
 CY United States  
 DT Journal; Article  
 FS 006 Internal Medicine  
 018 Cardiovascular Diseases and Cardiovascular Surgery  
 022 Human Genetics  
 LA English  
 SL English  
 ED Entered STN: 28 Apr 1999  
 Last Updated on STN: 28 Apr 1999  
 AB Background - The long-QT syndrome (LQTS) is a genetically heterogeneous disease in which 4 genes encoding ion-channel subunits have been identified. Most of the mutations have been determined in the transmembrane domains of the cardiac potassium channel genes KCNQ1 and HERG. In this study, we investigated the 3' part of \*\*\*HERG\*\*\* for \*\*\*mutations\*\*\*. Methods and Results - New specific primers allowed the amplification of the 3' part of HERG, the identification of 2 missense mutations, S818L and V822 M, in the putative cyclic nucleotide binding domain, and a 1-bp insertion, 3108+ 1G. Hypokalemia was a triggering factor for torsade de pointes in 2 of the probands of these families. Lastly, in a large family, a maternally inherited G to A transition was found in the splicing donor consensus site of HERG, 2592+ 1G-A, and a paternally inherited mutation, A341E, was identified in KCNQ1. The 2 more severely affected sisters bore both mutations. Conclusions - The discovery of mutations in the C-terminal part of HERG emphasizes that this region plays a significant role in cardiac repolarization. Clinical data suggests that these mutations may be less malignant than mutations occurring in the pore region, but they can become clinically significant in cases of hypokalemia. The first description of 2 patients with double heterozygosity associated with a dramatic malignant phenotype implies that genetic analysis of severely affected young patients should include an investigation for >1 mutation in the \*\*\*LQT\*\*\* genes.
- L4 ANSWER 18 OF 36 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN  
 AN 1999:172172 BIOSIS  
 DN PREV199900172172  
 TI Homozygous deletion in KVLQT1 associated with Jervell and Lange-Nielsen syndrome.  
 AU Chen, Qiuyun; Zhang, Danmei; Gingell, Robert L.; Moss, Arthur J.; Napolitano, Carlo; Priori, Silvia G.; Schwartz, Peter J.; Kehoe, Eileen; Robinson, Jennifer L.; Schutze-Bahr, Eric; Wang, Qing; Towbin, Jeffrey A.
- [Reprint author]  
 CS Department of Pediatrics (Cardiology), Baylor College of Medicine, One Baylor Plaza, Room 333E, Houston, TX, 77030, USA  
 SO Circulation, (March 16, 1999) Vol. 99, No. 10, pp. 1344-1347. print. CODEN: CIRCZ. ISSN: 0009-7322.  
 DT Article  
 LA English  
 ED Entered STN: 5 May 1999  
 Last Updated on STN: 5 May 1999  
 AB Background-Long-QT ( \*\*\*LQT\*\*\* ) syndrome is a cardiac disorder that causes syncope, seizures, and sudden death from ventricular arrhythmias, specifically torsade de pointes. Both autosomal dominant \*\*\*LQT\*\*\* (Romano-Ward syndrome) and autosomal recessive \*\*\*LQT\*\*\* (Jervell and Lange-Nielsen syndrome, JLNS) have been reported. Heterozygous mutations in 3 potassium channel genes, KVLQT1, KCNE1 (minK), and HERG, and the cardiac sodium channel gene SCN5A cause autosomal dominant \*\*\*LQT\*\*\*. Autosomal recessive \*\*\*LQT\*\*\*, which is associated with deafness, has been found to occur with homozygous mutations in KVLQT1 and KCNE1 in JLNS families in which QTc prolongation was inherited as a dominant trait. Methods and Results-An Amish family with clinical evidence of JLNS was analyzed for mutations by use of single-strand conformation polymorphism and DNA sequencing analyses for mutations in all known \*\*\*LQT\*\*\* genes. A novel homozygous 2-bp deletion in the S2 transmembrane segment of KVLQT1 was identified in affected members of this Amish family in which both QTc prolongation and deafness were inherited as recessive traits. This deletion represents a new JLNS-associated mutation in KVLQT1 and has deleterious effects on the KVLQT1 potassium channel, causing a frameshift and the truncation of the KVLQT1 protein. In contrast to previous reports in which \*\*\*LQT\*\*\* was inherited as a clear dominant trait, 2 parents in the JLNS family described here have normal QTc intervals (0.43 and 0.44 seconds, respectively). Conclusions-A novel homozygous KVLQT1 mutation causes JLNS in an Amish family with deafness that is inherited as an autosomal recessive trait.
- L4 ANSWER 19 OF 36 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN  
 AN 1999:186447 BIOSIS  
 DN PREV199900186447  
 TI Dominant mechanisms in \*\*\*LQT\*\*\* \*\*\*mutations\*\*\* of \*\*\*HERG\*\*\*  
 AU Kagan, A. [Reprint author]; Qin, D.; Zhen, M.; Fishman, G. I.; McDonald, T. V.  
 CS Albert Einstein Col. Med., New York, NY, USA  
 SO Biophysical Journal, (Jan., 1999) Vol. 76, No. 1 PART 2, pp. A417. print. Meeting Info.: Forty-third Annual Meeting of the Biophysical Society. Baltimore, Maryland, USA. February 13-17, 1999.  
 CODEN: BIOJAU. ISSN: 0006-3495.  
 DT Conference; (Meeting)  
 Conference; Abstract; (Meeting Abstract)  
 Conference; (Meeting Poster)  
 LA English  
 ED Entered STN: 5 May 1999  
 Last Updated on STN: 5 May 1999
- L4 ANSWER 20 OF 36 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 7  
 AN 1999212014 EMBASE  
 TI Dysfunction of delayed rectifier potassium channels in an inherited cardiac arrhythmia.  
 AU Sanguinetti M.C.  
 CS Dr. M.C. Sanguinetti, University of Utah, Eccles Institute of Human Genetics, 15 N 2030 E, Salt Lake City, UT 84112-5330, United States. mike.sanguinetti@hci.utah.edu  
 SO Annals of the New York Academy of Sciences, (1999) Vol. 868, pp. 406-413.  
 Refs: 55  
 ISSN: 0077-8923 CODEN: ANYAA  
 CY United States  
 DT Journal; Conference Article  
 FS 005 General Pathology and Pathological Anatomy  
 018 Cardiovascular Diseases and Cardiovascular Surgery  
 022 Human Genetics  
 029 Clinical Biochemistry  
 LA English  
 SL English  
 ED Entered STN: 8 Jul 1999  
 Last Updated on STN: 8 Jul 1999  
 AB The rapid (IKr) and slow (IKs) delayed rectifier K+ currents are key regulators of cardiac repolarization. HERG encodes the K(r) channel, and KVLQT1 and hminK encode subunits that coassemble to form K(s) channels. Mutations in any one of these genes cause Romano-Ward syndrome, an autosomal dominant form of long QT syndrome ( \*\*\*LQT\*\*\* ). \*\*\*Mutations\*\*\* in KVLQT1 and \*\*\*HERG\*\*\* are the most common cause of \*\*\*LQT\*\*\*. Not all missense \*\*\*mutations\*\*\* of \*\*\*HERG\*\*\* or KVLQT1 have the same effect on K+ channel function. Most mutations result in a dominant-negative effect, but the severity of the resulting phenotype varies widely, as judged by reduction of current induced by coexpression of wild-type and mutant subunits in heterologous expression systems. Mutations in hminK (S74L, D76N) reduce IK(s) by shifting the voltage dependence of activation and accelerating channel deactivation. A recessive form of \*\*\*LQT\*\*\* is caused by mutations in either KVLQT1 or

hminK. The functional consequences of mutations in delayed rectifier K<sup>+</sup> channel subunits are delayed cardiac repolarization, lengthened QT interval, and an increased risk of torsade de pointes and sudden death.

L4 ANSWER 21 OF 36 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

AN 1999:187485 BIOSIS

DN PREV199900187485

TI Multiple mechanisms of HERG current suppression in LQT2.

AU Hiraoka, M. [Reprint author]; Nakajima, T. [Reprint author]; Furukawa, T. [Reprint author]; Katayama, Y. [Reprint author]; Tanaka, T.; Itoh, T.; Nagai, R.; Sakurada, H.; Nakamura, Y.

CS Medical Research Institute, Tokyo Med and Dent Univ, Tokyo, Japan  
SO Biophysical Journal, (Jan., 1999) Vol. 76, No. 1 PART 2, pp. A75. print. Meeting Info.: Forty-third Annual Meeting of the Biophysical Society. Baltimore, Maryland, USA. February 13-17, 1999.  
CODEN: BIOJAU. ISSN: 0006-3495.

DT Conference; (Meeting)  
Conference; Abstract; (Meeting Abstract)  
Conference; (Meeting Poster)

LA English

ED Entered STN: 5 May 1999

Last Updated on STN: 5 May 1999

L4 ANSWER 22 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN

AN 1999:203136 CAPLUS

DN 131:68710

TI Identification of a novel \*\*\*HERG\*\*\* gene \*\*\*mutation\*\*\* by PCR-SSCP and cloning analyses

AU Yang, Ping; Armstrong, Martin; Dai, Dezai; Paulussen, Aimee; Luyten, Walter

CS Research Division of Pharmacology, China Pharmaceutical University, Nanjing, 210009, Peop. Rep. China

SO Zhongguo Yaoke Daxue Xuebao (1999), 30(1), 66-68  
CODEN: ZHYXE9; ISSN: 1000-5048

PB Zhongguo Yaoke Daxue

DT Journal

LA English

AB To investigate genetic risk factor of Long QT Syndrome (LQTS), \*\*\*mutations\*\*\* of \*\*\*HERG\*\*\* gene were screened in individuals susceptible to \*\*\*LQT\*\*\* and healthy controls by PCR based SSCP anal. A PCR based cloning assay was also developed and used to identify the mutation. An abnormal conformer was found in one healthy control by SSCP screening. This mutation was not able to be identified by direct sequencing. To sep. the mutated allele, the authors transformed it into plasmid and the final sequencing suggested it is a heterozygous 9 base pairs insertion at position 752 of HERG cDNA sequence (5'.fwdarw.3'). This mutation results in a Gly-Ala-Gly insertion in amino acid sequence. Unlike other mutations previously reported, the nine base pairs insertion is not a genetic risk factor of LQTS.

RE.CNT. 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

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AN 1999071874 EMBASE

TI N-linked glycosylation sites determine HERG: Channel surface membrane expression.

AU Petrecca K.; Atanasiu R.; Akhavan A.; Shrier A.

CS A. Shrier, Department of Physiology, McGill University, 3655 Drummond Street, Montreal, Que. H3G 1Y6, Canada. ashrier@physio.mcgill.ca

SO Journal of Physiology, (15 Feb 1999) Vol. 515, No. 1, pp. 41-48. .  
Refs: 26

ISSN: 0022-3751 CODEN: JPHYA7

CY United Kingdom

DT Journal; Article

FS 002 Physiology

018 Cardiovascular Diseases and Cardiovascular Surgery

022 Human Genetics

029 Clinical Biochemistry

LA English

SL English

ED Entered STN: 11 Mar 1999

Last Updated on STN: 11 Mar 1999

AB 1. Long QT syndrome ( \*\*\*LQT\*\*\* ) is an electrophysiological disorder that can lead to sudden death from cardiac arrhythmias. One form of \*\*\*LQT\*\*\* has been attributed to mutations in the human ether-a-go-go-related gene (HERG) that encodes a voltage-gated cardiac K<sup>+</sup> channel. While a recent report indicates that \*\*\*LQT\*\*\* in some patients is associated with a \*\*\*mutation\*\*\* of \*\*\*HERG\*\*\* at a consensus extracellular N-linked glycosylation site (N629), earlier studies failed to identify a role for N-linked glycosylation in the functional expression of voltage-gated K<sup>+</sup> channels. In this study we used pharmacological agents and site-directed mutagenesis to assess the contribution of N-linked glycosylation to the surface localization of HERG channels. 2. Tunicamycin, an inhibitor of N-linked glycosylation, blocked normal surface membrane expression of a HERG-green fluorescent protein (GFP) fusion protein (HERG(GFP)) transiently expressed in human embryonic kidney (HEK 293) cells imaged with confocal microscopy. 3. Immunoblot analysis revealed that N-glycosidase F shifted the molecular mass of HERG(GFP) stably expressed in HEK 293 cells, indicating the presence of

N-linked carbohydrate moieties. Mutations at each of the two putative extracellular N-linked glycosylation sites (N598Q and N629Q) led to a perinuclear subcellular localization of HERG(GFP) stably expressed in HEK 293 cells, with no surface membrane expression. Furthermore, patch clamp analysis revealed that there was a virtual absence of HERG current in the N-glycosylation mutants. 4. Taken together, these results strongly suggest that N-linked glycosylation is required for surface membrane expression of HERG. These findings may provide insight into a mechanism responsible for LQT2 due to N-linked glycosylation-related \*\*\*mutations\*\*\* of \*\*\*HERG\*\*\*.

L4 ANSWER 24 OF 36 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 9

AN 1998282827 EMBASE

TI HERG channel dysfunction in human long QT syndrome. Intracellular transport and functional defects.

AU Zhou Z.; Gong Q.; Epstein M.L.; January C.T.

CS C.T. January, Dept. of Medicine (Cardiology), Univ. of Wisconsin Hospital/Clinics, 600 Highland Ave., Madison, WI 53792, United States. ctj@medicine.wisc.edu

SO Journal of Biological Chemistry, (14 Aug 1998) Vol. 273, No. 33, pp. 21081-21066. .

Refs: 41

ISSN: 0021-9258 CODEN: JBCHA3

CY United States

DT Journal; Article

FS 018 Cardiovascular Diseases and Cardiovascular Surgery

022 Human Genetics

LA English

SL English

ED Entered STN: 17 Sep 1998

Last Updated on STN: 17 Sep 1998

AB \*\*\*Mutations\*\*\* in \*\*\*HERG\*\*\* are associated with human chromosome 7-linked congenital long QT ( \*\*\*LQT\*\*\* -2) syndrome. We used electrophysiological, biochemical, and immunohistochemical methods to study the molecular mechanisms of HERG channel dysfunction caused by \*\*\*LQT\*\*\* -2 mutations. Wild type \*\*\*HERG\*\*\* and \*\*\*LQT\*\*\* -2 \*\*\*mutations\*\*\* were studied by stable and transient expression in HEK 293 cells. We found that some mutations (Y611H and V822M) caused defects in biosynthetic processing of HERG channels with the protein retained in the endoplasmic reticulum. Other mutations (I593R and G628S) were processed similarly to wild type \*\*\*HERG\*\*\* protein, but these \*\*\*mutations\*\*\* did not produce functional channels. In contrast, the T474I \*\*\*mutation\*\*\* expressed \*\*\*HERG\*\*\* current but with altered gating properties. These findings suggest that the loss of HERG channel function in \*\*\*LQT\*\*\* -2 mutations is caused by multiple mechanisms including abnormal channel processing, the generation of nonfunctional channels, and altered channel gating.

L4 ANSWER 25 OF 36 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 10

AN 1998272678 EMBASE

TI Genomic structure of three long QT syndrome genes: KVLQT1, HERG, and KCNE1.

AU Splawski I.; Shen J.; Timothy K.W.; Vincent G.M.; Lehmann M.H.; Keating M.T.

CS M.T. Keating, Eccles Institute of Human Genetics, University of Utah, 15 N 2030 E, Salt Lake City, UT 84112, United States.  
mark@howard.genetics.utah.edu

SO Genomics, (1 Jul 1998) Vol. 51, No. 1, pp. 86-97. .

Refs: 39

ISSN: 0888-7543 CODEN: GNMCEP

CY United States

DT Journal; Article

FS 018 Cardiovascular Diseases and Cardiovascular Surgery

022 Human Genetics

LA English

SL English

ED Entered STN: 27 Aug 1998

Last Updated on STN: 27 Aug 1998

AB Long QT syndrome ( \*\*\*LQT\*\*\* ) is a cardiac disorder causing syncope and sudden death from arrhythmias. \*\*\*LQT\*\*\* is characterized by prolongation of the QT interval on electrocardiogram, an indication of abnormal cardiac repolarization. \*\*\*Mutations\*\*\* in KVLQT1, \*\*\*HERG\*\*\*, SCN5A, and KCNE1, genes encoding cardiac ion channels, cause

\*\*\*LQT\*\*\*. Here, we define the complete genomic structure of three \*\*\*LQT\*\*\* genes and use this information to identify disease-associated mutations. KVLQT1 is composed of 16 exons and encompasses approximately 400 kb. HERG consists of 16 exons and spans 55 kb. Three exons make up KCNE1. Each intron of these genes contains the invariant GT and AG at the donor and acceptor splice sites, respectively. Intron sequences were used to design primer pairs for the amplification of all exons. Familial and sporadic cases affected by \*\*\*mutations\*\*\* in KVLQT1, \*\*\*HERG\*\*\*, and KCNE1 can now be genetically screened to identify individuals at risk of developing this disorder. This work has clinical implications for presymptomatic diagnosis and therapy.

L4 ANSWER 26 OF 36 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 11

AN 1998111183 EMBASE

TI Genetics, molecular mechanisms and management of long QT syndrome.

AU Wang Q.; Chen Q.; Towbin J.A.

CS Dr. Q. Wang, Dept. of Pediatrics (Cardiology), Baylor College of Medicine,  
One Baylor Plaza, Houston, TX 77030, United States. qwang@bcm.tmc.edu

SO Annals of Medicine, (1998) Vol. 30, No. 1, pp. 58-65. .

Refs: 63

ISSN: 0785-3890 CODEN: ANMDEU

CY United Kingdom

DT Journal; Article

FS 018 Cardiovascular Diseases and Cardiovascular Surgery

022 Human Genetics

037 Drug Literature Index

LA English

SL English

ED Entered STN: 23 Apr 1998

Last Updated on STN: 23 Apr 1998

AB Cardiac arrhythmias cause more than 300,000 sudden deaths each year in the  
USA alone. Long QT syndrome ( \*\*\*LQT\*\*\* ) is a cardiac disorder that  
causes sudden death from ventricular tachyarrhythmias, specifically  
torsade de pointes. Four \*\*\*LQT\*\*\* genes have been identified: KVLQT1  
(LQT1) on chromosome 11p15.5, HERG (LQT2) on chromosome 7q35-36,

SCN5A

(LQT3) on chromosome 3p21-24, and MinK (LQT5) on chromosome 21q22.

SCN5A

encodes the cardiac sodium channel, and \*\*\*LQT\*\*\* -causing mutations in  
SCN5A lead to the generation of a late phase of inactivation-resistant  
whole-cell inward currents. Mexiletine, a sodium channel blocker, is  
effective in shortening the QT interval corrected for heart rate (QTc) of  
patients with SCN5A mutations. HERG encodes the cardiac I(Kr) potassium  
channel. \*\*\*Mutations\*\*\* in \*\*\*HERG\*\*\* act by a dominant-negative  
mechanism or by a loss-of-function mechanism. Raising the serum potassium  
concentration can increase outward HERG potassium current and is effective  
in shortening the QTc of patients with \*\*\*HERG\*\*\* \*\*\*mutations\*\*\* .  
KVLQT1 is a cardiac potassium channel protein that interacts with another  
small potassium channel MinK to form the cardiac I(Ks) potassium channel.  
Like \*\*\*HERG\*\*\* \*\*\*mutations\*\*\* , \*\*\*mutations\*\*\* in KVLQT1 and  
MinK can act by a dominant-negative mechanism or a loss-of-function  
mechanism. An effective treatment for \*\*\*LQT\*\*\* patients with KVLQT1  
or MinK mutations is expected to be developed based on the functional  
characterization of the I(Ks) potassium channel. Genetic testing is now  
available for some patients with \*\*\*LQT\*\*\* .

L4 ANSWER 27 OF 36 BIOSIS COPYRIGHT (c) 2006 The Thomson  
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AN 1998:522397 BIOSIS

DN PREV199800522397

TI "Touchdown vectorette-PCR": An efficient method for establishing unknown  
intronic sequences of \*\*\*LQT\*\*\* genes.

AU Rubie, C. [Reprint author]; Schutze-Bahr, E. [Reprint author]; Myriam, B.;  
Wedekind, H. [Reprint author]; Haverkamp, W. [Reprint author]; Moennig, G.  
[Reprint author]; Mergenthaler, J. [Reprint author]; Borggrefe, M.  
[Reprint author]; Assmann, G.; Breilhardt, G. [Reprint author]; Guicheney,  
P.; Funke, H.

CS Inst. Arteriosclerosis Res., Muenster, Germany

SO European Heart Journal, (Aug., 1998) Vol. 19, No. ABST. SUPPL., pp. 39.  
print.

Meeting Info.: XXth Congress of the European Society of Cardiology.  
Vienna, Austria. August 22-26, 1998. European Society of Cardiology.  
CODEN: EHJODF. ISSN: 0195-668X.

DT Conference; (Meeting)

Conference; Abstract; (Meeting Abstract)

Conference; (Meeting Poster)

LA English

ED Entered STN: 22 Dec 1998

Last Updated on STN: 22 Dec 1998

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AN 97318052 EMBASE

DN 1997318052

TI Multi-undulant T-U-wave, sinus bradycardia and long QT syndrome: A  
possible phenotype of mutant genes controlling the inward potassium  
rectifiers.

AU Shen C.-T.; Wu Y.-C.; Yu S.-S.-T.; Wang N.-K.

CS Dr. C.-T. Shen, Cathay General Hospital, Jen-Ai Road, Taipei,  
Taiwan, Province of China. ctsf0901@tpis5.seed.net.tw

SO Acta Paediatrica Sinica, (1997) Vol. 38, No. 4, pp. 267-275. .

Refs: 24

ISSN: 0001-6578 CODEN: CHEKAL

CY Taiwan, Province of China

DT Journal; Article

FS 007 Pediatrics and Pediatric Surgery

018 Cardiovascular Diseases and Cardiovascular Surgery

022 Human Genetics

LA English

SL English

ED Entered STN: 13 Nov 1997

Last Updated on STN: 13 Nov 1997

AB Inward rectifying potassium currents (1kr and 1ks) during phase 3  
repolarization of the myocyte from the beginning to the end of  
repolarization of the myocardial syncytium will inscribe a T-U-wave on the  
surface electrocardiogram (ECG). Type two congenital long QT syndrome  
(LQT2) is a phenotype of human ether-a-go-go-related gene ( \*\*\*HERG\*\*\* )  
\*\*\*mutation\*\*\* on the chromosome 7q 35-36. Type one congenital long QT

syndrome (LQT1) is a phenotype of KvLQT1 mutation on the chromosome  
11p15.5. Both LQT1 and LQT2 relate with inward rectifying potassium  
currents and is repolarization related, therefore, it is speculate that  
patients of LQT1 and LQT2 may have an abnormal T-U-wave on their surface  
ECG. To two probands of congenital \*\*\*LQT\*\*\* , 8 patients of  
structural heart disease treated by open heart surgery, 13 patients of  
structural heart disease without open-heart surgery, and 10 patients of  
normal controls, 24 hour-Holter monitoring was performed from July to  
December 1996. Their corrected QT interval (QTc) as well as the RR  
interval of every heart beat was calculated by a computer. The results  
showed that all 33 patients exhibited beat-by-beat fluctuation of their  
QTc and RR daily. The RR intervals of these two probands of congenital  
\*\*\*LQT\*\*\* were somewhere more than 1200 ms during circadian waking time,  
while 31 cases without \*\*\*LQT\*\*\* showed their RR prolongation only  
during the circadian sleeping time. A multi-undulant T-U-wave, or a  
beat-to-beat changing of vectors or amplitudes of their T-U-wave observed  
in these two probands of congenital \*\*\*LQT\*\*\* , were not observable in  
those 31 patients without congenital \*\*\*LQT\*\*\* . Therefore, we  
concluded that multi-undulant T-U-wave, sinus bradycardia and a longer QTc  
was a phenotype of the mutated genes which control the inward rectifying  
potassium currents during phase 3 repolarization.

L4 ANSWER 29 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN

AN 1997:185322 CAPLUS

DN 126:275543

TI Molecular bases for long QT syndrome ( \*\*\*LQT\*\*\* ): mutations in cardiac  
ion channel genes cause \*\*\*LQT\*\*\*

AU Nakajima, Tadashi; Keneko, Yoshiaki; Nagai, Kaneko

CS Dep. Internal Med. II, Gunma Univ. Sch. Med., Japan

SO Kokyu to Junkan (1997), 45(2), 121-128

CODEN: KOJUAJ; ISSN: 0452-3458

PB Igaku Shoin

DT Journal; General Review

LA Japanese

AB A review with 22 refs., on the theory of inherited long QT syndrome, and  
genetic factors and abnormal ion channels (i.e. KVLQT1, HERG, and SCN5A)  
in Romano-Ward syndrome.

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AN 96081969 EMBASE

DN 1996081969

TI Spectrum of HERG K+-channel dysfunction in an inherited cardiac  
arrhythmia.

AU Sanguinetti M.C.; Curran M.E.; Spector P.S.; Keating M.T.

CS EPHMBG, Cardiology Division, Univ. of Utah Health Sciences Center, Salt  
Lake City, UT 84112, United States

SO Proceedings of the National Academy of Sciences of the United States of  
America, (1996) Vol. 93, No. 5, pp. 2208-2212. .  
ISSN: 0027-8424 CODEN: PNASA6

CY United States

DT Journal; Article

FS 005 General Pathology and Pathological Anatomy

LA English

SL English

ED Entered STN: 2 Apr 1996

Last Updated on STN: 2 Apr 1996

AB Long QT syndrome ( \*\*\*LQT\*\*\* ) is an autosomal dominant disorder that  
can cause sudden death from cardiac arrhythmias. We recently discovered  
that \*\*\*mutations\*\*\* in \*\*\*HERG\*\*\* , a K+-channel gene, cause  
chromosome 7-linked \*\*\*LQT\*\*\* . Heterologous expression of HERG in  
Xenopus oocytes revealed that HERG current was similar to a  
well-characterized cardiac delayed rectifier K+ current, I(Kr), and led to  
the hypothesis that \*\*\*mutations\*\*\* in \*\*\*HERG\*\*\* reduced I(Kr),  
causing prolonged myocellular action potentials. To define the mechanism  
of \*\*\*LQT\*\*\* , we injected oocytes with mutant HERG complementary RNAs,  
either singly or in combination with wild-type complementary RNA. Some  
mutations caused loss of function, whereas others caused dominant negative  
suppression of HERG function. These mutations are predicted to cause a  
spectrum of diminished I(Kr) and delayed ventricular repolarization,  
consistent with the prolonged QT interval observed in individuals with  
\*\*\*LQT\*\*\* .

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AN 96160787 EMBASE

DN 1996160787

TI Missense mutation in the pore region of HERG causes familial long QT  
syndrome.

AU Benson D.W.; MacRae C.A.; Vesely M.R.; Walsh E.P.; Seidman J.G.;

Seidman

C.E.; Satter C.A.

CS Department of Cardiology, Children's Hospital, 300 Longwood Ave, Boston,  
MA

02115, United States

SO Circulation, (1996) Vol. 93, No. 10, pp. 1791-1795. .

ISSN: 0009-7322 CODEN: CIRCZA

CY United States

DT Journal; Article

FS 018 Cardiovascular Diseases and Cardiovascular Surgery

022 Human Genetics

LA English

SL English



ED Entered STN: 11 Jun 1996

Last Updated on STN: 11 Jun 1996

AB Background. Long QT syndrome ( \*\*\*LQT\*\*\* ) is an inherited cardiac disorder that results in syncope, seizures, and sudden death. In a family with \*\*\*LQT\*\*\*, we identified a novel mutation in human ether-a-go-go-related gene (HERG), a voltage-gated potassium channel. Methods and Results. We used DNA sequence analysis, restriction enzyme digestion analysis, and allele-specific oligonucleotide hybridization to identify the \*\*\*HERG\*\*\* \*\*\*mutation\*\*\*. A single nucleotide substitution of thymidine to guanine (T1961G) changed the coding sense of HERG from isoleucine to arginine (Ile593Arg) in the channel pore region. The mutation was present in all affected family members; the mutation was not present in unaffected family members or in 100 normal, unrelated individuals. Conclusions. We conclude that the Ile593Arg missense \*\*\*mutation\*\*\* in \*\*\*HERG\*\*\* is the cause of \*\*\*LQT\*\*\* in this family because it segregates with disease, its presence was confirmed in three ways, and it is not found in normal individuals. The Ile593Arg mutation may result in a change in potassium selectivity and permeability leading to a loss of HERG function, thereby resulting in \*\*\*LQT\*\*\*.

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AN 96278365 EMBASE

DN 1996278365

TI A \*\*\*mutation\*\*\* in \*\*\*HERG\*\*\* associated with notched T waves in long QT syndrome.

AU Dausse E.; Berthet M.; Denjoy I.; Andre-Fouet X.; Cruaud C.; Bennaceur M.; Faure S.; Coumel P.; Schwartz K.; Guicheney P.

CS INSERM UR153, Hopital Pitie-Salpetriere, Institut de Myologie, 47 boulevard de l'Hopital, 75013 Paris, France

SO Journal of Molecular and Cellular Cardiology. (1996) Vol. 28, No. 8, pp. 1609-1615.

ISSN: 0022-2828 CODEN: JMCDA

CY United Kingdom

DT Journal; Article

FS 005 General Pathology and Pathological Anatomy

018 Cardiovascular Diseases and Cardiovascular Surgery

022 Human Genetics

LA English

SL English

ED Entered STN: 7 Oct 1996

Last Updated on STN: 7 Oct 1996

AB Long QT syndrome ( \*\*\*LQT\*\*\* ) is a genetically heterogeneous inherited disorder that causes sudden death from cardiac arrhythmia. Four loci have been mapped to chromosomes 3, 4, 7 and 11 and three specific mutated genes for \*\*\*LQT\*\*\* syndrome have been identified. LQT2 results from mutations in the human ether-a-go-go-related gene, HERG, a cardiac potassium channel, whose protein product likely underlies I(Kr), the rapidly activating delayed rectifier current. By SSCP analysis and direct sequencing, we determined a new missense \*\*\*mutation\*\*\* in the \*\*\*HERG\*\*\* coding sequence, a G to A transition at position 1681 resulting in the substitution of threonine for a highly conserved alanine at codon 561. This mutation, Ala561Thr, in the coding sequence of the fifth membrane-spanning domain (S5) of the HERG protein seems to convey a risk of cardiac events in affected family members. In addition to a prolonged T wave of low amplitude on the surface ECG, a distinctive biphasic T-wave pattern was found in the left precordial leads of all affected subjects with the Ala561Thr mutation regardless of age, gender and beta blocking therapy.

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AN 96270661 EMBASE

DN 1996270661

TI Genetically defined therapy of inherited long-QT syndrome: Correction of abnormal repolarization by potassium.

AU Compton S.J.; Lux R.L.; Ramsey M.R.; Stetlich K.R.; Sanguinetti M.C.; Green L.S.; Keating M.T.; Mason J.W.

CS Division of Cardiology, Univ. of Utah Health Sciences Center, Salt Lake City, UT 84132-0001, United States

SO Circulation. (1996) Vol. 94, No. 5, pp. 1018-1022.

ISSN: 0009-7322 CODEN: CIRCZ

CY United States

DT Journal; Article

FS 018 Cardiovascular Diseases and Cardiovascular Surgery

037 Drug Literature Index

LA English

SL English

ED Entered STN: 1 Oct 1996

Last Updated on STN: 1 Oct 1996

AB Background: Many members of families with inherited long-QT ( \*\*\*LQT\*\*\* ) syndrome have \*\*\*mutations\*\*\* in \*\*\*HERG\*\*\*, a gene encoding a cardiac potassium channel that is modulated by extracellular potassium. We hypothesized that an increase in serum potassium would normalize repolarization in these patients. Methods and Results: We studied seven subjects with chromosome 7-linked \*\*\*LQT\*\*\* syndrome and five normal control subjects. Repolarization was measured by ECG and body surface potential mapping during sinus rhythm, exercise, and atrial pacing, before and after serum potassium increase. Potassium administration improved repolarization in the \*\*\*LQT\*\*\* syndrome. At baseline, \*\*\*LQT\*\*\* subjects differed from control subjects: resting corrected QT interval (QT(c), 627.±.90 versus 425.±.25 ms, P=.0007), QT(c) dispersion (133.±.62 versus 36.±.9 ms, P=.009), QT/RR slope (0.35.±.0.08 versus

0.24.±.0.07, P=.04) and global root-mean-square QT interval (RMS-QT(c); 525.±.68 versus 393.±.22, P=.002). All \*\*\*LQT\*\*\* subjects had biphasic or notched T waves. After administration of potassium, the \*\*\*LQT\*\*\* group had 24% reduction in resting QT(c) interval (from 617.±.92 to 469.±.23 ms, P=.004) compared with a 4% reduction among control subjects (from 425.±.25 to 410.±.45 ms, P>.05). The reduction was significantly greater in \*\*\*LQT\*\*\* subjects (P=.018). QT dispersion became normal in \*\*\*LQT\*\*\* subjects and did not change in control subjects. The slope of the relation between QT interval and cycle length (QT/RR slope) decreased toward normal. T-wave morphology improved in six of seven \*\*\*LQT\*\*\* subjects. The \*\*\*LQT\*\*\* group had a greater reduction in RMS-QT(c) than control subjects (P=.04). Conclusions: An increase in serum potassium corrects abnormalities of repolarization duration. T-wave morphology, QT/RR slope, and QT dispersion in patients with chromosome 7-linked \*\*\*LQT\*\*\*.

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AN 95081536 EMBASE

DN 1995081536

TI A molecular basis for cardiac arrhythmia: \*\*\*HERG\*\*\* \*\*\*mutations\*\*\* cause long QT syndrome.

AU Curran M.E.; Splawski I.; Timothy K.W.; Vincent G.M.; Green E.D.; Keating M.T.

CS Eccles Program in Human Molec. Biol., Department of Human Genetics, Univ. of Utah Health Sciences Center, Salt Lake City, UT 84112, United States

SO Cell. (1995) Vol. 80, No. 5, pp. 795-803.

ISSN: 0092-8674 CODEN: CELLB5

CY United States

DT Journal; Article

FS 005 General Pathology and Pathological Anatomy

018 Cardiovascular Diseases and Cardiovascular Surgery

022 Human Genetics

LA English

SL English

ED Entered STN: 29 Mar 1995

Last Updated on STN: 29 Mar 1995

AB To identify genes involved in cardiac arrhythmia, we investigated patients with long QT syndrome ( \*\*\*LQT\*\*\* ), an inherited disorder causing sudden death from a ventricular tachyarrhythmia, torsade de pointes. We previously mapped \*\*\*LQT\*\*\* loci on chromosomes 11 (LQT1), 7 (LQT2), and 3 (LQT3). Here, linkage and physical mapping place LQT2 and a putative potassium channel gene, HERG, on chromosome 7q35-36. Single strand conformation polymorphism and DNA sequence analyses reveal \*\*\*HERG\*\*\* \*\*\*mutations\*\*\* in six \*\*\*LQT\*\*\* families, including two intragenic deletions, one splice-donor mutation, and three missense mutations. In one kindred, the mutation arose de novo. Northern blot analyses show that HERG is strongly expressed in the heart. These data indicate that HERG is LQT2 and suggest a likely cellular mechanism for torsade de pointes.

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AN 95143848 EMBASE

DN 1995143848

TI A mechanistic link between an inherited and an acquired cardiac arrhythmia: HERG encodes the I(Kr) potassium channel.

AU Sanguinetti M.C.; Jiang C.; Curran M.E.; Keating M.T.

CS Eccles Human Molecular Biology Prog., Univ. of Utah Health Sciences Center, Salt Lake City, UT 84112, United States

SO Cell. (1995) Vol. 81, No. 2, pp. 299-307.

ISSN: 0092-8674 CODEN: CELLB5

CY United States

DT Journal; Article

FS 018 Cardiovascular Diseases and Cardiovascular Surgery

029 Clinical Biochemistry

LA English

SL English

ED Entered STN: 23 May 1995

Last Updated on STN: 23 May 1995

AB \*\*\*Mutations\*\*\* in \*\*\*HERG\*\*\* cause an inherited cardiac arrhythmia, long QT syndrome ( \*\*\*LQT\*\*\* ). To define the function of HERG, we expressed the protein in *Xenopus* oocytes. The biophysical properties of expressed HERG are nearly identical to the rapidly activating delayed rectifier K<sup>+</sup> current (I(Kr)) in cardiac myocytes. HERG current is K<sup>+</sup> selective, declines with depolarizations above 0 mV, is activated by extracellular K<sup>+</sup>, and is blocked by lanthanum. Interestingly, HERG current is not blocked by drugs that specifically block I(Kr) in cardiac myocytes. These data indicate that HERG proteins form I(Kr) channels, but that an additional subunit may be required for drug sensitivity. Since block of I(Kr) is a known mechanism for drug-induced cardiac arrhythmias, the finding that HERG encodes I(Kr) channels provides a mechanistic link between certain forms of inherited and acquired \*\*\*LQT\*\*\*.

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AN 95197880 EMBASE

DN 1995197880

TI Genetic approaches to cardiovascular disease: Supravalvular aortic stenosis, Williams syndrome, and long-QT syndrome.

AU Keating M.T.

CS Eccles Institute of Human Genetics, University of Utah, Building 533, Salt



Lake City, UT 84112, United States  
 SO Circulation, (1995) Vol. 92, No. 1, pp. 142-147 .  
 ISSN: 0009-7322 CODEN: CIRCAZ  
 CY United States  
 DT Journal; Article  
 FS 006 Internal Medicine  
 018 Cardiovascular Diseases and Cardiovascular Surgery  
 022 Human Genetics  
 LA English  
 SL English  
 ED Entered STN: 18 Jul 1995  
 Last Updated on STN: 18 Jul 1995

AB Background: Although family history can be an important risk factor for cardiovascular disease, relatively little is known about the nature of specific genetic risk factors. One approach to this problem is to identify and characterize genes responsible for inherited disorders in the hope that this information will also provide mechanistic insight into common forms of cardiovascular disease. Methods and Results: Over the last decade, it has become possible to identify genes that cause human disease by use of the techniques of molecular genetics, specifically genetic linkage analysis, positional cloning, and mutational analyses. We have used these techniques to study three inherited cardiovascular disorders: supravulvular aortic stenosis, Williams syndrome, and long-QT syndrome. We have discovered that the vascular pathology of supravulvular aortic stenosis and Williams syndrome results from mutations involving the elastin gene on chromosome 7q11.23. These mutations include intragenic deletions, translocations, and complete deletion of the elastin gene, suggesting that a quantitative reduction in elastin during vascular development is pathogenically important. To date, only the elastin gene has proved important for supravulvular aortic stenosis. By contrast, genetic linkage analyses in families with long-QT syndrome indicate that at least four distinct genes can cause this disorder. We have identified three \*\*\*LQT\*\*\* loci: LQT1 on chromosome 11p15.5, LQ72 on 7q35-36, and LQT3 on 3p21-24. Recently, we demonstrated that mutations in a putative cardiac potassium channel gene, HERG, are responsible for the chromosome 7-linked form of long-QT syndrome, whereas mutations in the cardiac sodium channel gene SCN5A cause the chromosome 3-linked form of this disorder. \*\*\*HERG\*\*\* \*\*\*mutations\*\*\* and potassium channel biophysics suggest a dominant-negative molecular mechanism and reduced repolarization currents. By contrast, SCN5A mutations probably cause subtle alterations of cardiac sodium channel function and prolonged depolarizing currents. Conclusions: Molecular genetic analyses of long-QT syndrome, supravulvular aortic stenosis, and Williams syndrome have begun to unravel the mechanisms underlying these inherited disorders. Rapid genetic testing for Williams syndrome is now available using a simple cytogenetic test, fluorescence in situ hybridization, but additional work will be required for long-QT syndrome and autosomal-dominant supravulvular aortic stenosis. Improved diagnosis and mechanistic understanding of these disorders should lead to rational treatment and prevention.

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